2009-1270
(Serial No. 09/719,045)

United States Court of Appeals

for the

Federal Circuit

IN RE: ANDREW P. CHAPMAN and DAVID J. KING

Appeal from the United States Patent and Trademark Office, Board of Patent Appeals and Interferences

BRIEF OF APPELLANTS ANDREW P. CHAPMAN AND DAVID J. KING

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CERTIFICATE OF INTEREST

Counsel for the (petitioner) (appellant) (respondent) (appellee) (amicus) (name of party)

Appellants Chapman and King certify the following (use "None" if applicable; use extra sheets if necessary):

1. The full name of every party or amicus represented by me is:

Andrew Paul Chapman and David John King

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

UCB Pharma S.A.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

UCB Pharma S.A. is wholly-owned by UCB S.A.
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4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

Woodcock Washburn LLP - Doreen Yatko Trujillo and Ellen M. Klann

Cozen O'Connor P.C. – Doreen Yatko Trujillo

June 9, 2009
Date

Doreen Yatko Trujillo
Signature of counsel

Doreen Yatko Trujillo
Printed name of counsel

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STATEMENT OF RELATED CASES

No other appeal in or from the same proceeding was previously before this or any other appellate court. No case is known to counsel to be pending in this or any other court that will directly affect or be directly affected by this Court's decision in the pending appeal.

STATEMENT OF JURISDICTION

1. The statutory basis for jurisdiction of the Board of Patent Appeals and Interferences ("Board") for hearing the appeal of the examiner's rejection is 35 U.S.C. § 134.

2. The Board issued a Decision on Appeal on May 27, 2008 (A17) and a Decision on Request for Rehearing on December 11, 2008 (A23). The Board's Decision on Request for Rehearing constitutes a final decision of the Board.

3. The appeal is timely, as the Notice of Appeal was filed by Express Mail on February 10, 2009 with the General Counsel of the United States Patent & Trademark Office ("USPTO"), the USPTO confirmed timely filing with the submission of the Certified Index on March 23, 2009, and this case was docketed at this Court on March 25, 2009. *See,* 35 U.S.C. § 142.

4. This Court has jurisdiction pursuant to 28 U.S.C. §1295 (a)(4)(A) and 35 U.S.C. § 141.

STATEMENT OF THE ISSUE

Whether the Board erred as a matter of law in finding the subject matter of claims 1, 13, and 14 of Application Serial No. 09/719,045 ("the '045 application"), chosen by the Board as representative of the claims on appeal, obvious over U.S. Patent No. 6,025,158 ("Gonzalez") alone or in combination with U.S. Patent No. 5,435,154 ("Barbanti") where the Board

a) misinterpreted the scope and content of Gonzalez;

b) erred in finding a lack of teaching away by Gonzalez; and

c) employed impermissible hindsight.

STATEMENT OF THE CASE

This is an appeal from rejections of claims 1-10 and 12-15 of the '045 application (A272-275). The examiner had issued a final rejection on March 29, 2006 based on two grounds (A245-46). First, the Examiner rejected claims 1-10 and 12-15 under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Gonzalez (A246). Second, the Examiner rejected claims 1 and 13-14 under 35 U.S.C. § 103(a) as unpatentable over Gonzalez in view of Barbanti (A248). Chapman appealed the final rejections to the Board (A261). The Board affirmed the Examiner's rejections for obviousness, but reversed the Examiner's anticipation rejection (A17). The Board denied Chapman's request for rehearing and this appeal followed (A20-23).

STATEMENT OF THE FACTS

Chapman filed the '045 application as a National Phase application of International Application Number PCT/GB99/01800, filed June 8, 1999 (A74). The '045 application claims priority to Application No. 9812545.3 filed in Great Britain on June 10, 1998 (A75).

I. The Technology

The technology in this appeal regards divalent antibody fragments. Divalent antibody fragments contain two antigen binding sites (A43). Whole antibodies are less than ideal for diagnosis and therapy, particularly diagnoses and therapy involving radioisotopes or drug conjugates, because of their size and long half-lives in the body (A29). For diagnosis, the long half-life of whole antibodies leads to decreased detection sensitivity; for therapy, the long half-lives lead to toxicity against normal tissue (A29). Antibody fragments are distributed more rapidly from the blood to tissues than whole antibodies, but are cleared much more rapidly from the circulation (A29).

II. The Invention

Applicants developed antibody fragments attached to polymers in a site-specific manner, resulting in a smaller size (i.e., for reaching tissues) and a clearance rate that is intermediate that of the whole antibodies and the fragments alone (A42; A56; A62). The claims are directed to divalent antibody fragments

comprising two antibody heavy chains (A31) and at least one polymer molecule that increases the circulating half-life of the fragment (A30; A51) attached to the heavy chains in a site-specific manner on each chain (A31) outside the variable region domain of each chain (A31). The site-specific attachment prevents a loss of binding affinity as compared to attachment that is not site-specific (A31; A49-50). Claim 1 of the '045 application is duplicated below:

> A divalent antibody fragment comprising two antibody heavy chains and at least one polymer molecule effective for increasing the circulating half-life of said fragment in covalent linkage, each heavy chain being covalently linked to the other by at least one non-disulphide interchain bridge linking the sulphur atom of a cysteine residue in one chain to the sulphur atom of a cysteine residue in the other chain, said cysteine residues being located outside of the variable region domain of each chain, characterised in that the at least one non-disulphide interchain bridge contains the at least one covalently linked polymer molecule.

(A272). All other pending claims depend from claim 1 (A272-275).

III. The Cited References

A. Gonzalez

The application that issued into Gonzalez was filed February 20, 1998 (A411). Gonzalez issued February 15, 2000 (A411) and comprises 206 columns (A648) and 136 sheets of 69 figures (A547). Gonzalez describes conjugates formed by attachment of antibody fragments to non-proteinaceous polymers with an apparent size of at least 500 kDa (A411). At column 11, lines 30-62, Gonzalez describes various antibody fragments including F_V, Fab, Fab', Fab'-SH, and

$F(ab')_2$ (A553). Fab, Fab', and Fv fragments have a single antigen-binding site; $F(ab')_2$ has two antigen-combining sites (A553, col. 11, lines 30-65). At column 19, lines 56-65, Gonzalez describes antibody fragments in which polymer attachment is targeted to the hinge region and states that, in a preferred embodiment, cysteine residue(s) are engineered into the hinge region to couple the polymer to a specific location (A557). At column 21, lines 35-50, Gonzalez describes preferred embodiments comprising antibody fragments selected from the group consisting of Fab, Fab', and Fab'-SH wherein every polymer molecule is attached to the hinge region of the fragment (A558). Regarding divalent antibody fragments, Gonzalez describes a preferred embodiment comprising no more than two polymer molecules, wherein each polymer molecule is attached to a cysteine residue on either the heavy or light chain of an $F(ab')_2$ antibody fragment that would normally form a disulfide bridge linking the two chains, but specifies that the disulfide bridge is avoided by substituting another amino acid for the corresponding cysteine residue in the opposite chain (A558, at col. 21, ll. 50-59; *see also* A559, at col. 23, ll 17 through col. 24 ll. 27; and A563-64, at col. 31, ll. 55 through col. 33, ll. 2). At column 35, lines 45-48, Gonzalez describes two antibody fragments linked together by polymer molecules to form a dumbbell-shaped structure, but does not specify how and where the antibody molecules are linked by the polymer molecules, or what fragments are to be used (A565). In the

same passage, Gonzalez describes conjugates containing two or more antibody fragments using polymer molecules derivatized with "multiple functional groups" to permit the attachment of two or more antibody fragments to the polymer backbone. (A565, at col. 35, ll. 53-57). Gonzalez identifies multiple crosslinking sites on the antibody fragments that can be used to make the conjugates including N-terminal amino groups, epsilon amino groups found on lysine residues, amino groups, imino groups, carboxyl groups, sulfhydryl groups, hydroxyl groups, and other hydrophilic groups (A568, at col. 41, ll. 63 through col. 42, ll 23). In one of the working examples, Gonzalez describes linking polyethylene glycol ("PEG") to the hinge of a Fab' (A607-09, col. 120, l. 15 through col. 123, l. 15). In another working example, Gonzalez describes generating pegylated $F(ab')_2$ by attaching the PEG to a lysine (A609-610, col. 123, l. 15 through col. 125, l. 60).

B. Barbanti

Barbanti describes the use of antibodies against TNF-alpha for *in vivo* treatment (A348). As the focus of this appeal will be upon Gonzalez, Barbanti will not be discussed further.

IV. Prosecution Before the Examiner

The examiner rejected claims 1-7, 12-13, and 15 as anticipated by Gonzales under 35 U.S.C. § 102(e) and rejected claims 1 and 13-14 as obvious over Gonzalez in view of Barbanti under 35 U.S.C. § 103(a) (A173-175) in a second-

action final rejection (A167-168). Claims 8-9 were withdrawn from consideration as allegedly being directed to a separate invention (A168). The examiner argued that claims 1-7, 12-13, and 15 were "entirely anticipated" by Gonzalez (A173). The examiner alleged that Gonzalez discloses embodiments in which

> two or more Fab, Fab' or Fab'-SH fragments are covalently conjugated to a polymer backbone. The polymer thus links the antibody fragments. See especially col. 35, lines 40-57; col. 41, lines 41-62. A preferred site of conjugating the polymer to the antibody fragments is at the hinge region of the latter; see col. 35, lines 6-13. In embodiments in which the number of Fab, Fab' or Fab'-SH fragments is two and the number of polymer members is one, instant claims 1-3 are anticipated.

(A173-174; A565; A568).

In response, Chapman amended claim 1 to specify that the polymer was part of the interchain bridge between the two heavy chains (A185). Chapman argued that the claims were not anticipated because Gonzalez does not disclose such an antibody (A194) and that the passage regarding the hinge region being a preferred site, i.e., col. 35, lines 6-13, referred to monovalent fragments only (A194-195). Chapman further argued that all the discussions in Gonzalez of divalent antibody fragments in which the polymer is attached to a cysteine report that the interchain bridge is "avoided entirely" by substituting one of the cysteines that would normally form a bridge with a serine (A195) and that the two specific examples discussing divalent antibody fragments describe attaching the polymer to a lysine (A195). Finally, Chapman argued that the passages cited by the examiner that

specifically describe divalent antibody fragments do not specify where on the antibody the polymer is to be attached expressly or inherently (A195), and that the passage cited by the examiner regarding attachment to the hinge was directed to monovalent fragments (A196). Chapman argued that Barbanti did not overcome the deficiencies of Gonzalez (A197). Chapman requested that claims 8 and 9 be rejoined, noting that they depend from pending claim 7 (A189).

The examiner issued an advisory action refusing to enter the amendment, arguing that it raised new issues, and advising Chapman that the amendment would not be entered upon appeal (A200-201).

Chapman filed a Request for Continued Examination ("RCE") (A206), resubmitting the prior amendment and arguments (A209; A219-221).

The examiner issued a non-final office action in response to the RCE (A224-225), maintaining the prior rejections over Gonzalez, but revising the rejection over Gonzalez alone to be a rejection for anticipation under 35 U.S.C. § 102(e) or, alternatively, for obviousness under 35 U.S.C. § 103(a) (A227). The examiner added claims 8 and 9 to the rejection over Gonzalez alone (A227). The examiner basically repeated the arguments advanced previously in the final rejection (A228). In response to Chapman's argument that the teachings of adding the polymer to the hinge of Fab' or Fab'-SH fragments regard monovalent, not divalent fragments, the

examiner cited applicants' own examples to show that two Fab' fragments are cross-linked to make the divalent antibody fragments (A231).

In their response, Chapman again argued that Gonzalez does not disclose the claimed invention expressly or inherently (A239-240) and noted that Gonzalez discussed preparing the dumbbell-shaped structures using multiple functional groups, which suggested multiple attachment locations (A240). Regarding obviousness, Chapman argued that there was no motivation to prepare the claimed invention and that Gonzalez actually teaches away from the claimed invention by instructing that an interchain bridge between chains is to be avoided (A241). Chapman again argued that Barbanti does not overcome the deficiencies of Gonzalez (A241-242).

The examiner issued a second final rejection (A245), maintaining the rejections over Gonzalez basically for the reasons stated previously (A247-249). The examiner acknowledged that Gonzalez does not discuss coupling the polymer to cysteines in the hinge region in the same section as it discusses the dumbbell-shaped structure, but argued that the claimed invention was obvious because it was "within the 4 corners of the reference" (A247-248). The examiner accused Chapman of obfuscating the issues by arguing passages from Gonzalez that contradicted the examiner's arguments, i.e., that Gonzalez describes the use of multiple functional groups for attaching the fragments to the polymers and the use

of multiple linking sites within the antibody fragments themselves (A248). The examiner addressed Chapman's teaching away argument by accusing Chapman of highlighting one genre of embodiments while ignoring others (A248).

Chapman filed a request for a pre-appeal brief conference with a notice of appeal (A253-257). Chapman argued that the USPTO had to rely upon inherency to support the rejection over Gonzalez alone for anticipation, and that this was error because inherency is not based upon possibilities or probabilities (A254). Chapman also argued that "within the 4 corners of the reference" is not the correct standard for measuring inherency (A255), nor is it the appropriate standard for measuring obviousness (A255). Chapman further argued that the USPTO had not made out a *prima facie* case of obviousness by failing to provide motivation to make the claimed invention (A255). Finally, Chapman argued that Gonzalez teaches away from the claimed invention because it describes derivatizing the polymer with multiple functional groups as well as using a variety of cross-linking agents for attachment of the fragments and, additionally, teaches away from having the polymer form an interchain bridge (A255-256).

The decision on the pre-appeal conference advised Chapman to proceed with the appeal because at least one actual issue for appeal remained, without stating which issue(s); the rejection of claims 1-10 and 12-15 was maintained (A260).

Chapman filed an appeal brief thereafter (A261). Chapman again argued that claims 1-10, 12-13, and 15 were not anticipated by nor rendered obvious over Gonzalez (A265) and that claims 1 and 13-14 were not obvious over Gonzalez in view of Baranti (A269). Chapman basically expanded upon its prior arguments throughout prosecution, as set forth above. Chapman again argued that Gonzalez did not anticipate the claimed invention, either expressly or inherently (A265-266). Chapman again argued that Gonzalez actually teaches away from the claimed invention (A267) and that the USPTO had not made out a *prima facie* case of obviousness (A267-268). Chapman further argued that the USPTO had inappropriately used hindsight to reconstruct the claimed invention (A268-269). Chapman again argued that Barbanti did not overcome the deficiencies of Gonzalez (A269). The appeal brief was 11 pages, excluding the appendices (A271).

The examiner filed a 21-page Examiner's Answer in response to Chapman's Appeal Brief (A279; A299). The examiner basically reiterated his prior arguments with a notable addition. The examiner argued that

> [i]t is reasonable to take the position that one who is considering what Gonzales et al anticipate would have arrived at the instant invention by listing of all of the possibilities that can result when one chooses from among the various kinds of conjugate constructs (with respect to the number and type of antibody fragment(s)) and the number of polymer molecules) taught by Gonzales et al, in combination with all of the various kinds of coupling/linking chemistry taught by Gonzales et al.

(A289-290). As the excerpt from the Examiner's Answer below indicates, the examiner took the position that one would have been led to the claimed invention.

> Further, among all of the listed possibilities, one would have been more particularly led to those that involve attachment of the fragments to the polymer via a hinge region cysteine residue, since Gonzales et al teach that a preferred site of conjugating the polymer to the antibody fragment is at the hinge region of the latter (col. 19, lines 56-65 and col. 35, lines 6-13) and that a most preferred site of attachment therein is a cysteine residue. See, for example, col. 19, lines 56-65. Thus what is claimed is inherently within the "4 corners of the reference" even if it is not ipsis verbis disclosed. If these considerations have failed to show that Gonzales et al anticipate, then these considerations are to be taken as showing that Gonzales et al have shown what is claimed to have been obvious, as explained further infra.

(A290). The examiner further stated that the claimed structure would be achieved when one couples two of the Fab'-SH constructs taught to two activated sites on a polymer to form the dumbbell structure (A290-291). Regarding obviousness, the examiner argued that if one failed to arrive at the claimed invention, it would evidence less than ordinary skill in the art (A295).

Chapman filed a Reply Brief again emphasizing that the examiner's arguments did not comply with the standards for anticipation or obviousness, and noting that, to the extent the USPTO was relying upon the disclosure of the genus, i.e., the dumbbell-shaped structure, as disclosing the species, the case law

regarding anticipation of a species required that the species be "at once envisaged" (A302-305, specifically A304).

Chapman requested oral argument. During oral argument, Chapman emphasized that, even were one to follow the procedure in Gonzalez set forth for attaching the polymer to an Fab', one would not end up with the claimed invention as the procedures are different (A327). Chapman further emphasized that there are over 110 amino acids on each chain of the antibody fragments for attaching the polymer (A330).

V. The Board's Findings

The Board rendered a Decision on Appeal ("Decision') on May 27, 2008 (A2). The Board stated that claims 1, 13, and 14 were representative (A3).

A. The Board Reversed the Anticipation Rejection[1]

The Board stated that, when a generic disclosure serves as the basis for anticipation, one skilled in the art must be able to "at once envisage" the claimed structure in the disclosure (A12). The Board found that too much in the way of mental gymnastics would have been necessary for one of ordinary skill in the art to have "at once envisage[d]" the claimed invention based upon the different structures described in Gonzalez (A13). The Board noted the variety of linkages

[1] Curiously, the Board's discussion of anticipation followed the discussion of obviousness (A11). This seems to be putting the proverbial cart before the horse as one would generally analyze anticipation first. Accordingly, the discussion of anticipation is addressed first here.

available for crosslinking the polymer to the antibody, including amino, imino, carboxyl, sulfhydryl, hydroxyl, and other hydrophilic groups (A13). The Board further noted that Gonzalez fails to precisely define the dumbbell-structure and that its structure is open to interpretation – e.g., one could interpret the dumbbell-shaped structure as referring to the coupling of antibody fragments via (1) the heavy chain cysteine; (2) the light chains; or (3) linkages not involving the sulfhydryl group (-SH) of a cysteine residue (A13-14). The Board observed, thus, that linkage at the sulfhydryl group "is not the only choice for producing a dumbbell-shaped structure" (A14). Notably, citing the disclosure in Gonzalez teaching the elimination of one of two cysteine residues when placing the polymer between heavy and light chains of an $F(ab')_2$, the Board expressly rejected the examiner's assertion that, when Fab'-SH is utilized to form the dumbbell shape, persons skilled in the art would necessarily arrive at the claimed structure (A14). The Board noted the further choice as to whether to use the sulfhydryl group of both fragments, or just one (A14).

B. The Board Affirmed the Obviousness Rejections

1. Gonzalez Alone

The Board noted the examiner's acknowledgment that Gonzalez fails to provide an example of an antibody having the claimed structure. The Board then cited the examiner's findings that Gonzalez teaches (1) a dumbbell-shaped

antibody structure comprised of two monovalent Fab' fragments; (2) linking the monovalent Fab' fragments via a polymer molecule; and (3) that conjugating a polymer molecule to a hinge cysteine residue is a preferred embodiment to support that such teachings render the claimed invention obvious (A8). The Board noted, but rejected, Chapman's argument that Gonzalez teaches away from the claimed antibody because Gonzalez expressly discusses attaching polymer molecules to a cysteine residue on one chain of a divalent antibody fragment and substituting the corresponding cysteine residue in the opposite chain with another amino acid (A8). In support, the Board noted Gonzalez' statement that the conjugates are not limited to "any particular type of linkage between an antibody fragment and a polymer" (A8-9). In light of this statement, the Board did not find the prior statement as teaching away (A9).

The Board argued that Gonzalez describes two distinct embodiments of divalent antibodies: (1) the one noted by Chapman in which the polymer is linked between the light and heavy chains and only one cysteine residue is present, and (2) the dumbbell-shaped structure (A9). The Board said that the second antibody type is clearly an alternative to the first and that, rather than having the polymer hold the heavy and light chains together as for the former, the polymer joins the two fragments (A9). The Board then agreed with the examiner that Gonzalez would have led to the claimed structure using the hinge cysteine residues because

of the preference for a polymer in the hinge region (A9). While acknowledging that Gonzalez does not explicitly teach how to make the dumbbell-shaped structure, the Board cited what it believed to be "clear guideposts" for making the dumbbell-shaped structure – bifunctional linkers, Fab' conjugated to PEG via a cysteine, and a teaching that a polymer attached to the hinge region is stable (A10). The Board stated, thus, that a "likely path a person of ordinary skill would take in making a dumbbell-shaped antibody structure would have been to link the disclosed Fab' fragments at the cysteine residues using the bifunctional linker" (A10). The Board dispensed with Chapman's arguments regarding hindsight based upon the foregoing (A10).

Finally, the Board stated that, while there is no express teaching of how to make the structure, a person of ordinary skill coupled with Gonzalez' teachings "would have suggested the claimed structure as a solution to the **problem**" (A11, emphasis added). The Board does not, however, state to what problem it is referring (A11).

2. Gonzales, in View of Barbtanti

The Board addressed this obviousness rejection after the rejection for anticipation (A15). The Board noted that Gonzalez states "PEG attached to the sulfhydryl group in the hinge region of a Fab' fragment reduced clearance compared to the parental Fab' molecule" (A16). The Board relied on an implicit

showing of suggestion, teaching or motivation, namely, the knowledge of one of ordinary skill in the art and the nature of the problem as a whole, to substantiate its finding that a person of skill in the art would have modified Barbanti's antibody with PEG to extend its serum half-life so more of it would bind to TNF-alpha, thereby increasing its efficacy (A16).

VI. Chapman's Request for Rehearing

Chapman requested rehearing under 37 C.F.R. § 41.52 (A334). Chapman questioned why the Board found the necessary picking and choosing to preclude a finding of anticipation, but not a finding of obviousness (A335). Chapman stated that there is not a finite number of identified predictable solutions, noting the Board's acknowledgement of the choices regarding linkage groups on the antibody fragments and regarding the different types of antibody fragments that could be used for the dumbbell-shaped structure (A335-336). Chapman also pointed out that, assuming an Fab' fragment as the starting point, there are potentially 500 locations (amino acids) at which to attach the polymer on each Fab' (A336). Chapman also pointed out that the Board's argument against teaching away contradicted its argument that one would prefer to attach the polymer to a hinge region cysteine (A336).

The Board denied the request for rehearing (A23). Notably, the Board stated that Chapman's assertion that the Board acknowledged that different types of

antibody fragments that could be used in the dumbbell-shaped structure was incorrect (A23). This appeal followed.

SUMMARY OF THE ARGUMENT

The Board erred as a matter of law in finding representative claims 1, 13, and 14 obvious over Gonzalez alone or in view of Baranti. The Board's decision was based upon several factual findings that are not supported by substantial evidence.

First, the Board misinterpreted the scope of Gonzalez. Specifically, the Board found that Gonzalez discloses a dumbbell-shaped structure made of two monovalent Fab' fragments; that Gonzalez discloses a divalent fragment in which the polymer is linked between the light and heavy chains; and suggested that Gonzalez limits the type of fragments which are to be used in the dumbbell-shaped structure. Chapman contends that none of these findings is supported by any evidence, much less substantial evidence.

Second, the Board erred by finding that Gonzalez does not teach away from Chapman's invention. The Board relied on general disclosure to counter Chapman's arguments based upon disclosure relevant to divalent antibody fragments. Chapman contends that the Board's finding is not supported by substantial evidence.

Finally, substantial evidence does not support the Board's alleged finding of motivation to make the claimed invention. The Board referred to a problem that was not described. The Board, rather, employed impermissible hindsight in finding Chapman's invention obvious.

ARGUMENT

I. Standard of Review

The Board's legal conclusions are reviewed without deference; the Board's factual findings are reviewed for substantial evidence. *Hitzeman v. Rutter*, 243 F.3d 1345, 1353-54 (Fed. Cir. 2001). Substantial evidence "means such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *Consol. Edison Co. v. NLRB*, 305 U.S. 197, 229 (1938) (citing *Appalachian Elec. Power v. NLRB*, 93 F.2d 985, 989 (4th Cir. 1938)).

II. The Board Erred as a Matter of Law in Finding Obviousness

Whether an invention would have been obvious is a legal question based on underlying findings of fact including (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness. *In re Gartside,* 203 F.3d 1305, 1316 (Fed. Cir. 2000) (citing, ultimately, *Graham v. John Deere Co.*, 383 U.S. 1, 17–8 (1966)). Because the Board relied upon fact-findings that are not supported by substantial evidence and employed impermissible

hindsight in making its obviousness determinations, the Board erred as a matter of law in finding Chapman's claims obvious. Barbanti does not overcome the deficiencies in Gonzalez. Accordingly, the discussion below focuses upon the Board's findings regarding Gonzalez.

A. The Board Misinterpreted the Scope and Content of Gonzalez

The Board's findings regarding the scope and content of Gonzalez are not supported by substantial evidence.

1. Gonzalez Does Not Disclose a Dumbbell-Shaped Structure Made of Two Monovalent Fab' Fragments

Citing Fact Findings ("FF") 8 and 12 of the Decision, the Board stated that the examiner found that Gonzalez teaches a dumbbell-shaped antibody structure comprised of two monovalent Fab' fragments and describes linking them via a polymer molecule (A8). The Board, however, misconstrued FF 8 and 12. Neither Fact Finding indicated that Gonzalez discloses a dumbbell-shaped structure comprising Fab' fragments (A6-7).

Regardless, Gonzalez does not disclose such a structure. At column 35, lines 45-48, Gonzalez describes two antibody fragments linked together by a polymer molecule to form a dumbbell-shaped structure, but does not specify how and where the antibody molecules are linked by the polymer molecules, or what fragments are to be used (A565; A10). At column 21, lines 35-50, Gonzalez describes preferred embodiments comprising antibody fragments selected from the

group consisting of Fab, Fab', and Fab'-SH wherein every polymer molecule is attached to the hinge region of the fragment (A558). What Gonzalez does not describe is dumbbell-shaped structures comprising Fab'.

This finding by the Board is not supported by any evidence, much less substantial evidence.

2. Gonzalez Does Not Disclose a Divalent Fragment in Which the Polymer Is Linked Between the Light and Heavy Chains

The Board stated that one of two divalent antibody embodiments described in Gonzalez has the polymer hold the heavy and light chains together, citing FF 7 of the examiner (A9). The Board has characterized the examiner's Fact Finding correctly (A5). Unfortunately, the examiner's FF7 is incorrect. Citing column 21, lines 50-59 of Gonzalez, the examiner states that Gonzalez describes conjugates containing an "$F(ab')_2$ antibody fragment in which the polymer is **attached between** the disulphide bridge that would ordinarily link the heavy and lights chains" (A5, emphasis added). The cited passage is duplicated below.

> **In yet another preferred embodiment, the conjugate contains a $F(ab')_2$ antibody fragment attached to no more than about 2 polymer molecules, wherein every polymer molecule is attached to a cysteine residue in the light or heavy chain of the antibody fragment that would ordinarily form the disulfide bridge linking the light and heavy chains, wherein the disulfide bridge is avoided by substituting another amino acid, such as serine, for the corresponding cysteine residue in the opposite chain.**

(A558). Both the examiner and the Board are misinterpreting this passage -- the polymer is not linking the heavy and light chain; it is attached to one **or** the other, not both. Considering that the disulfide bridge is avoided by substituting another amino acid for the cysteine in the opposite chain, the implication is clearly that the polymer is not linking the heavy and light chain.

This finding by the Board is not supported by any evidence, much less substantial evidence.

3. Gonzalez Does Not Limit Which Fragments Are to Be Used in the Dumbbell-Shaped Structure

In FF3, the Board stated that the antibody can be a monovalent Fab fragment, a monovalent Fab' which includes one or more cysteines in the constant region, or an $F(ab')_2$ that has a hinge cysteine between the Fab' fragments (A5). Gonzalez actually describes five antibody fragments that can be used in the conjugates including F_V, Fab, Fab', Fab'-SH, and $F(ab')_2$ (A553, col. 11, lines 30-66). In the Request for Rehearing, Chapman noted what it believed to be the Board's acknowledgement of the choices regarding the different types of antibody fragments that could be used for the dumbbell-shaped structure, citing FF3 (A336). In the Decision on Request for Rehearing, however, the Board stated that Chapman's assertion that the Board acknowledged that different types of antibody fragments could be used in the dumbbell-shaped structure was incorrect (A23). The Board argued that FF3 generally referred to fragments

which could be conjugated to PEG and that there was no reference to the dumbbell structure (A23). But, the passage in Gonzalez referring to the dumbbell-shaped structures makes no reference to the type of fragments to be used (A565). Chapman contends, thus, that any fragment could be used, including an $F(ab')_2$. Indeed, if an $F(ab')_2$ were used, it would be tetravalent as comprising two divalent fragments.

Substantial evidence does not support the Board's finding that it was incorrect to say that different types of fragments could be used in the dumbbell-shaped structure.

B. Substantial Evidence Does Not Support the Board's Finding of No Teaching Away

A prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention. *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1547, 1550 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Whether or not a reference teaches away from the claimed invention is a question of fact. *In re Napier*, 55 F.3d 610, 613 (Fed. Cir. 1995). The Board's finding regarding no teaching away is not supported by substantial evidence.

First, Gonzalez suggests making dumbbell structures using polymer molecules derivatized with "multiple functional groups" to permit the attachment of two or more antibody fragments to the polymer backbone (A565, at col. 35, ll. 45-57). The use of multiple functional groups suggests multiple attachment

locations, not the same location on each heavy chain, much less a cysteine residue on each heavy chain. Indeed, Gonzales lists a variety of crosslinking sites on the antibody fragments that can be used, e.g., N-terminal amino groups and epsilon amino groups found on lysine residues, amino groups, imino groups, carboxyl groups, sulfhydryl groups, hydroxyl groups, and other hydrophilic groups (A568, at col. 41, ll. 63-57).

Second, when Gonzales discusses attaching a polymer to a divalent antibody fragment, i.e., $F(ab')_2$, it specifically states that disulfide bridges are avoided by substituting another amino acid for the corresponding cysteine residue in the opposite chain (A558; A559; A563-564). Although Gonzalez is referring to the bridge between the heavy and light chains it, nonetheless, is teaching away from using the polymer as a bridge.

The Board did not address Chapman's argument regarding the suggestion of multiple functional groups being a teaching away. In response to Chapman's argument regarding the avoidance of the disulphide bridge, the Board argued that Gonzalez explicitly states that antibody conjugates can be produced using any suitable technique and any type of linkage, citing column 19, lines 19-24 (A8; A557). The passage cited by the Board, however, is not specifically directed to divalent antibody fragments connected to polymers; Chapman's cited passages are.

Substantial evidence does not support the Board's finding of no teaching away.

C. The Board Employed Impermissible Hindsight

"A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007) (citing *Graham*, 383 U.S. at 36). As this Court recently reemphasized, a flexible teaching, suggestion, motivation test is the "primary guarantor against a non-statutory hindsight analysis." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008). A flexible test ensures that the obviousness test proceeds on the basis of evidence arising before the time of the invention as the statute requires. *Id.* at 1365. Whether a person of ordinary skill in the art would have been motivated to combine references is a question of fact. *In re Gartside*, 203 F.3d at 1316. The Board inappropriately used hindsight in finding Chapman's claimed invention obvious.

Citing *KSR*, the Board acknowledged that, once the differences between the prior art and the claimed invention are identified, the next step is to identify a reason persons of ordinary skill in the art would have been prompted to combine the prior art to make the claimed invention (A7). The Board failed to identify a reason to make the claimed invention, however. Although the Board argued that a

person of ordinary skill coupled with Gonzalez' teachings "would have suggested the claimed structure as a solution to the **problem**" (A11, emphasis added), the Board never identified the problem. Neither did the Board identify a design need or market pressure to come up with the claimed invention. *KSR*, 550 U.S. at 421.

Indeed, the only apparent motivation for making Chapman's claimed invention is the single sentence in the Gonzalez patent regarding the preparation of a dumbbell-shaped structure (A9). Based upon this single sentence, and its misinterpretation of Gonzalez as disclosing a dumbbell-shaped structure comprising two Fab' fragments, the Board felt the only issue remaining was whether persons skilled in the art would have had **reason** to join the two Fab' fragments together using a polymer linked to the hinge region cysteine (A9, emphasis added). The Board was wrong.

First, the Board has provided no motivation for making the dumbbell-shaped structure described in Gonzalez, much less Chapman's claimed invention. The Board simply observed that Gonzalez "expressly describes" the dumbbell-shaped antibody structure (A9). This description is not sufficient, however, to show motivation to make Chapman's claimed invention. The Gonzalez patent has over 132 columns of text, excluding the Sequence Listing and claims (A613-614). Each column has about 65 lines for a total of over 8,800 lines of text. The passage regarding the dumbbell-shaped structure is only four lines long (A565, col. 35, ll.

45-48). Further, nothing in Gonzalez even suggests that dumbbell-shaped fragments are desired. Indeed, as the Board acknowledged, Gonzalez reports that the conjugates prepared improved the circulating half life (A4, citing Abstract of Gonzalez, A411). Second, Gonzalez does not disclose a dumbbell-shaped structure comprising monovalent Fab' fragments.

Chapman contends that substantial evidence does not support a finding of motivation to make their invention. Rather, one of skill in the art would only arrive at using monovalent Fab' fragments to make a dumbbell-shaped structure using their disclosure as a guide. The Board's arguments against anticipation over Gonzalez support Chapman's contention.

In their analysis of anticipation, the Board noted the variety of linkages available for crosslinking the polymer to the antibody, including amino, imino, carboxyl, sulfhydryl, hydroxyl, and other hydrophilic groups (A13). The Board further noted that Gonzalez fails to precisely define the dumbbell-structure and that its structure is open to interpretation – e.g., one could interpret the dumbbell-shaped structure as referring to the coupling of antibody fragments via (1) the heavy chain cysteine; (2) the light chains; or (3) linkages not involving the sulfhydryl group (-SH) of a cysteine residue (A13-14). Citing the disclosure in Gonzalez teaching the elimination of one of two cysteine residues when placing the polymer between heavy and light chains of an $F(ab')_2$, the Board expressly

rejected the examiner's assertion that, when Fab'-SH is utilized to form the dumbbell shape, persons skilled in the art would necessarily arrive at the claimed structure (A14). The Board clearly thought the number of variables precluded a finding of anticipation, but somehow did not think they precluded a finding of obviousness. Quite the contrary, the Board's anticipation analysis is extremely relevant to, and actually undermines, its obviousness conclusions.

Assuming that motivation to prepare the dumbbell-shaped structure is found, which Chapman does not concede, the Board must still show why one of ordinary skill in the art would be led to Chapman's invention. Even if obvious to try is the standard applied, the Board must still show that there is a finite number of identified, predictable solutions. *KSR*, 550 U.S. at 421. As the Board's anticipation analysis evidences, there is not a finite number of identified predictable solutions for making the dumbbell-shaped structure. When one adds to the Board's anticipation analysis the fact that Gonzalez describes five different fragments that can be used (A553), and the number of potential locations on each fragment to attach the polymer, i.e., 500 (A336), the number of solutions is actually infinite.

In its obviousness assessment, the Board refers to what it calls "clear guideposts" in Gonzalez for how to make the dumbbell-shaped structure (A10). With the exception of the bifunctional linkers, however, the alleged guideposts the

Board refers to are not related to the dumbbell-shaped structure (A10). Although the Board challenged Chapman's assertion that any fragment could be used because the passages describing fragments did not refer to the dumbbell-shaped structure (A23), it did not hesitate to use passages that did not refer to the dumbbell-shaped structure to support its obviousness determination. Such is clearly an impermissible use of hindsight. *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to depreciate the claimed invention.")

The Board clearly employed impermissible hindsight in finding Chapman's invention obvious.

CONCLUSION

For the foregoing reasons, Chapman respectfully request this Court to reverse the Board's decision of May 27, 2008 finding Chapman's claimed invention obvious over Gonzalez and obvious over Gonzalez in view of Barbanti.

Respectfully Submitted,

Dated: June 9, 2009

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ADDENDUM

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A (Rev. 04/07)

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ANDREW PAUL CHAPMAN and DAVID JOHN KING

Appeal 2008-0454
Application 09/719,045
Technology Center 1600

Decided: May 27, 2008

Before TONI R. SCHEINER, LORA M. GREEN, and
RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal from the final rejection of claims 1-10 and 12-15. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

The claims are directed to a divalent antibody comprised of two heavy chains linked together by a polymer. The polymer is characterized in the

claim as effective for increasing the circulating half-life of the antibody.

Claims 1-10 and 12-15 stand rejected (App. Br. 3) as follows:

1) Claims 1-10, 12, 13, and 15 under 35 U.S.C. § 102(e) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over Gonzalez (U.S. Pat. No. 6,025,158, Feb. 15, 2000) (Ans. 4); and

2) Claims 1, 13, and 14 under 35 U.S.C. § 103(a) as obvious over Gonzalez and Barbanti (U.S. Pat. No. 5,436,154, Jul. 25, 1995) (Ans. 6).

Claims 1, 13, and 14 are representative and read as follows:

> 1. A divalent antibody fragment comprising two antibody heavy chains and at least one polymer molecule effective for increasing the circulating half-life of said fragment in covalent linkage, each heavy chain being covalently linked to the other by at least one non-disulphide interchain bridge linking the sulphur atom of a cysteine residue in one chain to the sulphur atom of a cysteine residue in the other chain, said cysteine residues being located outside of the variable region domain of each chain, characterised in that the at least one non-disulphide interchain bridge contains the at least one covalently linked polymer molecule.
>
> 13. An antibody fragment according to Claim 1 which is able to selectively bind to a cell surface or soluble antigen.
>
> 14. An antibody fragment according to Claim 13 wherein the antigen is human tumour necrosis factor-α or a platelet derived growth factor or a receptor thereof.

REJECTIONS OVER GONZALEZ

Claims 1-10, 12, 13, and 15 stand rejected under 35 U.S.C. § 102(e) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over Gonzalez.

Claim 1

Claim 1 is directed to a divalent antibody fragment comprising two antibody heavy chains. A polymer molecule which is "effective for increasing the circulating half life" of the antibody is covalently linked to both chains. The claimed antibody has the following additional structural elements:

1) the heavy chains are covalently linked by at least one non-disulphide interchain bridge;

2) the non-disulphide interchain bridge links "the sulphur atom of a cysteine residue in one chain to the sulphur atom of a cysteine residue in the other chain" (i.e., the sulphur atoms are part of the bridge, but are not directly linked to each other);

3) at least one covalently linked polymer is present in the non-disulphide interchain bridge; and

4) the cysteine residues in the interchain bridge are located outside the variable region domain of each chain.

Scope and content of the prior art

The Examiner finds that Gonzalez describes all the limitations of the claimed antibody, or in the alternative, renders it obvious. The following findings of fact (FF) are pertinent to the Examiner's conclusion that the claimed antibody is not patentable over Gonzalez:

1. Gonzalez describes anti-IL-8 antibodies conjugated to a polymer, such as PEG, which improves the antibody's circulating half life (Gonzalez, Abstract; at col. 27, ll. 12-14; Ans. 5).

2. In its Background section, Gonzalez acknowledges that PEGylation has not been shown to extend the half-life of antibodies in certain prior art

references, but "PEG attached to the sulfhydryl group in the hinge region of a Fab' fragment reduced clearance compared to the parental Fab' molecule" (Gonzalez, at col. 1, ll. 30-43).

3. The antibody can be a monovalent Fab fragment, a monovalent Fab' fragment which includes one or more cysteine residues in the constant region, or an $F(ab')_2$ antibody fragment which has a hinge cysteine between the Fab' fragments (Gonzalez, at col. 11, ll. 57-66; Ans. 5)

4. The conjugates described by Gonzalez "can be made using any suitable technique . . . for derivatizing antibody fragments with polymers. It will be appreciated that the invention is not limited to conjugates utilizing any particular type of linkage between an antibody fragment and a polymer" (Gonzalez, at col. 19, ll. 19-24; Ans. 5).

5. In one embodiment, the polymer can be targeted to the hinge region of the parental antibody fragment, including preferred embodiments in which "a cysteine residue or residues is (are) engineered into the hinge region of the parental antibody fragment in order to couple polymer specifically to a selected location in the hinge region" (Gonzalez, at col. 19, ll. 56-65; at col. 21, ll. 36-40; Ans. 5).

6. For example, Gonzalez teaches linking PEG to the hinge of a Fab' heavy chain, a location which is outside the antibody variable region (Gonzalez, at cols. 120 to 123; particularly, at cols. 122, ll. 64 to 123, l. 3; Ans. 5).

7. Gonzalez also describes conjugates containing a $F(ab')_2$ antibody fragment in which the polymer is attached between the disulphide bridge that would ordinarily link the heavy and lights chains (Gonzalez, at col. 21, 50-59). In this embodiment, the polymer is attached to a cysteine in the light

or heavy chain; the cysteine in the opposite chain is replaced with another amino acid to avoid forming a disulphide bond between the chains (*id.*).

8. In another embodiment, Gonzalez describes antibody conjugates in which "a polymer molecule is used to link together two antibody fragments to form a dumbbell-shaped structure. . . Such structures can be made by using a polymer molecule derivatized with multiple functional groups permitting the direct attachment, or the attachment by means of bi- or multi-functional linkers, of two or more antibody fragments to the polymer backbone" (Gonzalez, at col. 35, ll. 45-57; at col. 41, ll. 41-43; *see* Ans. 5).

Rationale for prior art rejections over Gonzalez

9. The Examiner finds that the teaching in Gonzalez of a polymer molecule linking two antibody fragments together to form a dumbbell-shaped structure (FF 8) coupled to the disclosure of conjugating PEG to the hinge region of an Fab' heavy chain (FF 5, 6) anticipates the structure of the antibody in claim 1 (Ans. 5, 8, 10),

10. i.e., where the heavy chains are linked by a PEG molecule (the "polymer molecule" of claim 1) in an "interchain bridge" formed between the opposing heavy chain cysteine residues (*see Claim 1* above, structural elements 2) and 3)) are in a region outside the variable region domains (*see Claim 1* above, structural element 4)).

11. While there is no single exemplification of the claimed antibody structure, the Examiner finds that the claimed structure is within "the scope of what" Gonzalez teaches because a person of ordinary skill would have been necessarily led to it "among all of the listed possibilities" since "a preferred site of conjugating the polymer to the antibody fragment is at the hinge region" (Ans. 10-11, citing FF 5, 6, 8).

12. In regard to the obviousness of the claimed structure, the Examiner states there are explicit teachings of a dumbbell-shaped structure (FF 8) and a Fab' conjugated to PEG at the hinge region via a cysteine residue (FF 6).

13. Thus, the Examiner asserts, "[t]he only step that one of ordinary skill in the art would need to take is to realize that, when a polymer molecule [is] used to link together two antibody fragments to form a dumbbell-shaped structure, such linkage to each of the two antibody fragments could be formed by the type of coupling chemistry shown at col. 120, line 15-col. 122, line 31" which teaches PEG coupled to the hinge region of the heavy chain of Fab' (Ans. 15).

14. The Examiner finds that such modification would have within the skill of the ordinary artisan since it is one of the explicit and preferred types of coupling/linking chemistry taught by Gonzalez (*id.*).

Obviousness

The "examiner bears the initial burden, on review of the prior art . . , of presenting a prima facie case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). In making an obvious determination, the Examiner must first identity the scope and content of the prior art and then ascertain the differences between the prior art and the claimed invention. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Once the differences between the prior art and the claimed invention have been identified, the next step is to identify a reason why persons of ordinary skill in the art would have been prompted to combine the prior art to have made the claimed invention. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007).

In this case, the Examiner acknowledges there is no specific example of an antibody having the claimed antibody structure comprising a polymer that links cysteine residues, in an interchain bridge, of two opposing heavy chains as required by claim 1 (FF 11). However, the Examiner finds Gonzalez teaches a dumbbell-shaped antibody structure comprised of two monovalent Fab' fragments (FF 8, 12) and describes linking them via a polymer molecule (FF 8). The Examiner also finds that conjugating a polymer molecule to a hinge cysteine residue is a preferred embodiment (FF 5, 6, 11). Based on these teachings, the Examiner contends that it would have been obvious to have formed the dumbbell-shaped antibody by linking the Fab' fragments via the hinge cysteine-polymer structure, meeting the limitations of the claimed interchain bridge.

Appellants contend that the Examiner erred. They assert that Gonzalez teaches away from the claimed antibody because Gonzalez "specifically discusses attaching polymer molecules to a cysteine residue on one chain of a divalent antibody fragment" and substituting the "corresponding cysteine residue in the opposite chain" with another amino acid (App. Br. 6; Reply Br. 5-6; *see* FF 7). Thus, Appellants argue that Gonzalez would have led persons of ordinary skill in the art away from the claimed antibody structure comprising an interchain bridge which links "the sulphur atom of a cysteine residue in one to the chain to the sulphur atom of a cysteine residue in the other chain."

The Examiner has the better argument. Gonzalez explicitly states that antibody conjugates can be produced used any suitable technique and are not limited to "any particular type of linkage between an antibody fragment and a polymer" (FF 4; Gonzalez, at col. 19, ll. 19-24; *see* Ans. 5). Thus, while

Gonzalez describes $F(ab')_2$ antibodies in which the polymer is linked between light and heavy chains – with only one cysteine residue between them (FF 7) – we do not find that this "teaches away" from the claimed invention because Gonzalez expressly states that its conjugates are not limited to a particular linkage type (FF 4).

Gonzalez describes at least two distinct embodiments of divalent antibodies. First, Gonzalez describes a divalent antibody in which the polymer is linked between light and heavy chains and only one cysteine residue is present (FF 7; App. Br. 6). However, Gonzalez expressly describes another antibody structure in which "a polymer molecule is used to link together two antibody fragments to form a dumbbell-shaped structure" (FF 8; Gonzalez, col. 35, ll. 45-57; *see* Ans. 5). This second antibody type is clearly an alternative to the first since Gonzalez states that the polymer joins the two fragments together (FF 8), rather than having the polymer hold the heavy and light chains together as for the $F(ab')_2$ described in column 21 (FF 7). Thus, the only issue – as recognized by the Examiner – is whether persons of skill in the art would have had reason to join the fragments together using a polymer linked to the hinge cysteine residue (FF 13). We agree with the Examiner that Gonzalez would have led to this structure because of the preference for a polymer in the hinge region (FF 2, 5, 13).

In its Background section, Gonzalez refers to prior art which established that "PEG attached to the sulfhydryl group in the hinge region of a Fab' fragment reduced clearance compared to the parental Fab' molecule" (FF 2; Gonzalez, at col. 1, ll. 30-43). Consistent with this, Gonzalez also discloses attachment of a polymer to the hinge region (FF 5), and as pointed out by the Examiner, provides a complete working example in which a

polymer (PEG) is coupled to the cysteine of the heavy chain hinge region (FF 6, 9). Thus, persons of skill in the art would have recognized the advantages of placing PEG in the antibody hinge region.

Appellants' argument fails to acknowledge the dumbbell structure (FF 8) as a distinct and alternative embodiment from the $F(ab')_2$ antibody fragment at column 21, ll. 51-59 (FF 7). Gonzalez does not explicitly teach how to make the dumbbell-shaped structure, but Gonzalez provides clear guideposts, including descriptions of 1) bifunctional linkers to join the antibody fragments to make the dumbbell structure (FF 8); 2) Fab' fragments conjugated to PEG via a cysteine (FF 6); and 3) a teaching that a polymer attached to the hinge region is stable (FF 2). Thus, a likely path a person of ordinary skill would take in making a dumbbell-shaped antibody structure would have been to link the disclosed Fab' fragments at the cysteine residues using the bifunctional linker.

We do not agree that the Examiner relied upon "'hindsight reconstruction to pick and chose among isolated among isolated structures'" (App. Br. 8). Gonzalez's teaching of the dumbbell-shaped structure, without more guidance in how to make it, together with the disclosure of stable Fab' fragments with a polymer conjugated to a cysteine of the hinge region (FF 6), would have suggested to the ordinary skilled person that such Fab' fragments could be readily linked polymer to polymer using a bifunctional linker, as explicitly stated by Gonzalez when characterizing the dumbbell-shaped antibody structure (FF 8).

Precise teachings directed to the specific subject matter of a claim are not required to reach a conclusion of obviousness. *KSR*, 127 S. Ct. at 1741. "[T]he teaching, motivation, or suggestion may be implicit from the prior art

as a whole, rather than expressly stated in the references. . . . The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kahn*, 441 F.3d 977, 987-988 (Fed. Cir. 2006). Here, Gonzalez discloses an embodiment in which two antibody fragments are joined by a bifunctional linker (FF 8). While there is no express teaching in how to make this structure, the knowledge of a person of ordinary skill in the art coupled with the Gonzalez's teachings (i.e., FF 5, 6), would have suggested the claimed structure as a solution to the problem. A "person of ordinary skill is also a person of ordinary creativity, not an automaton." *KSR*, 127 S. Ct. 1727 at 1742.

Accordingly, we affirm the rejection of claim 1 as obvious over Gonzalez. Claims 2-10, 12, 13, and 15 fall with claim 1 because separate reasons for their patentability were not provides. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Anticipation

While there is no single exemplification of the claimed antibody structure, the Examiner finds that it is with "the scope of what" Gonzalez teaches because a person of ordinary skill would have been necessarily led to it "among all of the listed possibilities" since "a preferred site of conjugating the polymer to the antibody fragment is at the hinge region" (Ans. 10-11; FF 11). Specifically, the Examiner relies on the following evidence to establish anticipation:

- Gonzalez's teaching of a polymer conjugated to the cysteine of a monovalent Fab' (FF 5, 6)
- Gonzalez's description of a dumbbell shaped structure comprising at least two antibody fragments (FF 8).

The Examiner concludes:

> Gonzalez et al disclose embodiments in which two or more Fab, Fab' or Fab'-SH fragments are covalently conjugated to a polymer backbone. The polymer thus links the antibody fragments. See especially col. 35, lines 40-57 and col. 41, lines 41-62. See col. 35, lines 40-57, wherein there is a teaching of "a polymer molecule used to link together two antibody fragments to form a dumbbell-shaped structure." Such a "dumbbell-shaped structure" is consistent with the divalent antibody fragment of instant claim 1.

(Ans. 5).

The Examiner's case boils down to the following assertion: that the claimed antibody structure would necessarily be arrived at when an Fab'-SH fragment is utilized as a starting material to produce Gonzalez's dumbbell shaped divalent antibody structure (*see supra* at p. 11 quoting from Ans. 5).

Anticipation requires that every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim. *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001). A specific example is not required to establish anticipation. *See In re Petering*, 301 F.2d 676 (CCPA 1962); *In re Schaumann*, 572 F.2d 312, 316 (CCPA 1978); *Sanofi-Synthelabo v. Apotex Inc.*, 470 F.3d 1368, 1377 (Fed. Cir. 2006). However, when a generic disclosure is the basis for anticipation, one skilled in the art must be able to "at once envisage" the claimed structure in the disclosure. *Petering*, 301 F.2d. at 681.

In our opinion, although Gonzalez suggests the antibody structure of claim 1, too much in the way of mental gymnastics would have been necessary for persons of ordinary skill to have "at once envisage[d]" the claimed antibody structure among the different structures described in the Gonzalez patent.

As pointed out by Appellants, Gonzalez discloses crosslinking the polymer to the antibody through a variety of linkages, including through amino, imino, carboxyl, sulfhydryl, hydroxyl, and other hydrophilic groups (Gonzalez, at col. 41, l. 56 to col. 42, l. 23; *see* Reply Br. 5). Thus, while the sulfhydryl linkage is preferred in the context of a single Fab' fragment, there is the need for picking and choosing among the various possible crosslinking sites to produce a divalent antibody comprised of two Fab' fragments which are linked via a polymer at a hinge cysteine. An anticipatory "reference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference." *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972). In this case, because there are a number of different linkages to choose from, we find that the ordinary skilled artisan would not necessarily have envisaged the claimed structure upon reading the Gonzalez patent.

Furthermore, the dumbbell-shaped structure is not precisely defined or described in Gonzalez. Rather, it is open to interpretation and could be read to cover multiple structures, e.g. where the fragments are 1) coupled via the heavy chain cysteine as in claim 1; 2) coupled via their light chains; and 3) coupled via linkages not involving the sulfhydryl group (-SH) of a cysteine

residue. Thus, linkage at the sulfhydryl group is not the only choice for producing a dumbbell-shaped structure.

The Examiner asserts that, when Fab'-SH is utilized to form the dumbbell shape, persons of skill in the art would have "necessarily arrived at" the claimed structure in which the polymer acts as an interchain bridge linking the cysteine residues of each heavy chain (Ans. 11).

We do not agree. On one hand, Gonzalez describes engineering a cysteine residue into the hinge region for the purpose of coupling a polymer (FF 5), but, on the other hand, Gonzalez teaches eliminating one of two cysteine residues when placing the polymer between the heavy and light chains of an $F(ab')_2$ (FF 7). A person of ordinary skill who desired to utilize a hinge cysteine for coupling the polymer would have had the choice of: 1) coupling the polymer to a cysteine on one fragment and a non-cysteine residue on the other antibody fragment (e.g., to avoid forming a disulphide bridge between them (FF 7), or, alternatively, 2) using the hinge cysteine on each Fab' to form an interchain bridge with the polymer molecule. Thus, the determination of whether to use Fab'-SH to form the dumbbell-shaped antibody would entail choosing to use the sulfhydryl group of both Fab' fragments, rather than only one. Once again, picking and choosing would have been necessary to have arrived at the antibody structure of claim 1.

For the foregoing reasons, we do not agree that the antibody structure of claim 1 is anticipated by Gonzalez. We reverse the rejection of claims 1-10, 12, 13, and 15 as anticipated by Gonzalez.

REJECTION OVER GONZALEZ AND BARBANTI

Claims 1, 13, and 14 stand rejected under 35 U.S.C. § 103(a) as obvious over Gonzalez and Barbanti.

Claims 13 is directed to the antibody fragment of claim 1 "which is able to selectively bind to a cell surface or soluble antigen." Claim 14 further define the antigen of clam 13 as "human tumour necrosis factor-α [TNF-alpha] or a platelet derived growth factor or a receptor thereof."

The Examiner finds that Barbanti describes TNF-alpha antibodies for in vivo treatment (Ans. 6). The Examiner finds that persons of skill in the art would have had reason to conjugate these antibodies to PEG for the advantage of extending their half-life as taught in Gonzalez (Ans. 6-7). The Examiner also states that a person of ordinary skill in the art "would have been reasonably motivated to consider both references, because both IL-8 and TNF-alpha are involved in inflammation and because increasing the circulating half-life of an antibody to any mediator of inflammation would have been expected to permit more of the administered antibody to bind the mediator" (Ans. 7).

Appellants contend that 1) Gonzalez does not "provide motivation to couple any antibody fragment to a polymer such as PEG" because it does not generally teach PEG as useful to extend the half-life of any other antibody fragment (App. Br. 10). Appellants also argue that Barbanti 2) "gives absolutely no suggestion that serum half-life is considered to be a problem, or that longer serum half-lives are desired" (*id.*) and that 3) "the Office is focusing upon a single treatment. Barbanti . . . however, clearly contemplates multiple administrations over time" (*id.*).

We are not convinced by these arguments that the Examiner erred. Appellants take the Examiner to task for apparently misquoting Gonzalez's disclosure in column 1, lines 29-31, as teaching that PEG extends the half-life of antibodies, when it actually states that "PEGylation has not been shown to extend serum half-life [of antibodies] to useful levels" (Gonzalez, at col. 1, ll. 29-31; App. Br. 9-10). However, later in the same paragraph, Gonzalez states that "PEG attached to the sulfhydryl group in the hinge region of a Fab' fragment reduced clearance compared to the parental Fab' molecule" (FF 2; Gonzalez, at col. 1, ll. 30-43) – the same configuration as claimed. Moreover, Gonzalez shows this to be the case for its own antibody. Thus, we agree with the Examiner that Gonzalez's teachings would be recognized as generally teaching that PEG extends the half-life of antibodies, regardless of what was stated in its background section (Ans. 17). Appellants have not provided evidence to rebut the Examiner's reasonable findings.

It is not necessary for there to be an explicit suggestion in Barbanti to utilize PEG to enhance the half-life of its antibody. A suggestion, teaching, or motivation to combine the relevant prior art teachings does not have to be found explicitly in the prior art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *Kahn*, 441 F.3d at 987-988. In this case, the Examiner provides a well-reasoned statement for why persons of skill in the art would have had reason to modify Barbanti's antibody with PEG: to extend its serum half-life so more of it will be present to bind to TNF-alpha (Ans. 7), thereby increasing its efficacy. The Examiner also notes that both

IL-8 (Gonzalez) and TNF-alpha (Barbanti) are each involved inflammation and thus the references are in the same field of art (Ans. 7). These are not "conclusory statements" as characterized by Appellants (Reply Br. 6), but statements based on fact and reasoning. The Examiner argues, and we agree, that persons of skill in the art would have recognized the advantages of utilizing PEG upon reading Gonzalez. We are not persuaded by Appellants' that the Examiner's reasoning is flawed.

We do not see any merit in Appellants' argument about single treatments versus multiple treatments (App. Br. 10). In either case, the Examiner's reasoning about improving serum half life of antibody would be applicable. Moreover, the Examiner points to disclosure in Barbanti of single administrations (Ans. 19-20). Thus, we do not see any deficiency in the Examiner's statement of the rejection.

For the foregoing reasons, we affirm the rejections of claims 13 and 14 as obvious over Gonzalez and Barbanti.

CONCLUSION

In summary, we affirm the rejections of claims 1-10, 12, 13, and 15 as obvious over Gonzalez and claims 1, 13, and 14 as obvious over Gonzalez in view of Barbanti. We reverse the rejection of claims 1-10, 12, 13, and 15 as anticipated by Gonzalez.

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

lp

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Please find below and/or attached an Office communication concerning this application or proceeding.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ANDREW PAUL CHAPMAN and DAVID JOHN KING

Appeal 2008-0454
Application 09/719,045
Technology Center 1600

Decided: December 11, 2008

Before TONI R. SCHEINER, LORA M. GREEN, and
RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON REQUEST FOR REHEARING

Appellants have requested rehearing of the decision entered May 27, 2008 ("Decision"), which affirmed rejections of claims 1-10 and 12-15 (all of the pending claims) for obviousness. The request for rehearing is denied.

DISCUSSION

Appellants argue that "the failure to find nonobviousness under the present circumstances was erroneous" (Req. Reh'g 2). According to Appellants, "the number of possibilities that one needs to pick and choose from" precludes a finding of obviousness (*id.*). Appellants also argue that the prior art Gonzalez patent teaches away from a disulphide bridge in the claimed divalent antibody fragment (*id.* at 3).

These arguments do not "state with particularity the points believed to have been misapprehended or overlooked by the Board," as required by 37 C.F.R. § 41.52. Essentially, Appellants disagree with the conclusions reached in the Decision. That is not a proper basis for a Request for Rehearing. For an applicant dissatisfied with the outcome of a Board decision, the proper course of action is to appeal, not to file a Request for Rehearing to re-argue issues that have already been decided. *See* 35 U.S.C. §§ 141, 145.

In their Appeal Brief, Appellants argued, as they do in this Request for Rehearing, that Gonzalez "lists a variety of crosslinking sites on that antibody fragments that can be used" to attach the polymer molecules (App. Br. 7) (Req. Reh'g 3 ("Because the polymer can be attached to either chain, there are potentially 500 locations at which the linkage could occur **on each fragment**")).

This argument was expressly addressed in the Decision. We acknowledged that different linkages were described in Gonzalez (Dec. 7-8).

However, based on the evidence described in Findings of Fact (FF)[1] 2, 5, 6, and 9, we concluded that persons of skill in the art would have recognized the advantages of coupling PEG to the cysteine of the heavy chain hinge region, thereby form a disulphide bridge as required by the claims (Dec. 8-9). We also addressed Appellants' argument regarding picking and choosing (Dec. 9). Appellants have not identified anything we misapprehended or overlooked in our Decision. Instead, they merely reiterate their earlier arguments.

Appellants contend that we misstated the Examiner's argument: "the Examiner never argued that there were teachings of a dumbbell shaped antibody structure comprised of two monovalent Fab' fragments" (Req. Reh'g 3).

Our statement regarding the Examiner's argument referenced: 1) FF8 which directly quotes from Gonzalez's description of the "dumbbell-shaped [antibody] structure," 2) FF12 which refers to the Examiner's finding of an Fab' conjugated to a PEG via a cysteine residue, and 3) page 5 (*see* FF8 and Dec. 8) of the Answer which explains the Examiner's position that Gonzalez's teachings would have led persons of ordinary skill in the art to link Fab'-SH fragments to form the dumbbell structure (Dec. 7-8). Thus, in context, our characterization of the Examiner's argument would have been understood to include Gonzalez's explicit description, as well as what it would have reasonably suggested to persons of ordinary skill in the art. Consistently, we summarized the Examiner's position as follows: "Based on these teachings, the Examiner contends that it would have been obvious to

[1] "Findings of Fact" refer to the Findings of Fact set forth in the Decision.

have formed the dumbbell-shaped antibody by linking the Fab' fragments via the hinge cysteine-polymer structure, meeting the limitations of the claimed interchain bridge" (Dec. 7).

Appellants also argue that "the Board acknowledged, the fragments that could be involved in the dumbbell shaped structure include Fab, Fab', and $F(ab')_2$ (Decision, finding of fact 3)" (Req. Reh'g 3). This is not correct. Finding of Fact 3 generally referred to fragments which could be conjugated to the PEG polymer; there was no reference to the dumbbell shape. To the contrary, we explicitly distinguished the dumbbell structure from alternative structures formed from the $F(ab')_2$ antibody fragment (Dec. 9:4-14).

Finally, we already considered, but were not persuaded by Appellants' argument that Gonzalez teaches away from the claimed invention (Dec. 7-8).

Since Appellants have not pointed out any points that we overlooked or misunderstood, we decline to modify our earlier conclusions.

REHEARING DENIED

cdc

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CERTIFICATE OF SERVICE

United States Court of Appeals
for the Federal Circuit
No. 2009-1270
----------)

IN RE ANDREW P. CHAPMAN and DAVID J. KING

----------)

I, Elissa Matias, being duly sworn according to law and being over the age of 18, upon my oath depose and say that:

Counsel Press was retained by COZEN O' CONNOR, Attorneys for Appellants, to print this document. I am an employee of Counsel Press.

On the **9th Day of June 2009**, I served the **BRIEF OF APPELLANTS ANDREW P. CHAPMAN and DAVID J. KING** within upon:

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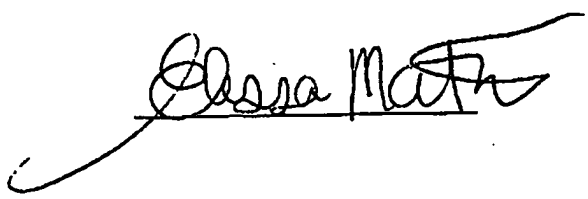
June 9, 2009



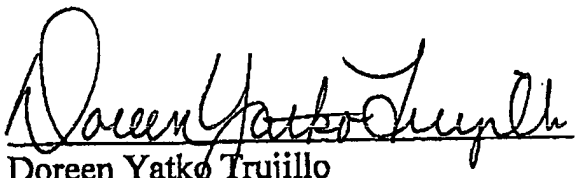
CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B), because it contains 6,223 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

This brief complies with the typeface requirements of the Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of the Federal Rule of Appellate Procedure 32(a)(6), because it has been prepared in a proportionally spaced typeface using Microsoft Word 2003 in Times New Roman 14 point font.

Dated: June 9, 2009

Respectfully submitted,



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